Journal Pre-proof

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PII: S0960-0760(19)30058-5

DOI: https://doi.org/10.1016/j.jsbmb.2019.105489

Reference: SBMB 105489

To appear in: *Journal of Steroid Biochemistry and Molecular Biology*

Received Date: 3 March 2019

Revised Date: 31 July 2019

Accepted Date: 30 September 2019

Please cite this article as: { doi: https://doi.org/

Vitamin D microencapsulation and fortification: Trends and technologies

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Highlights:

- Vitamin D synthesis and absorption is reviewed.
- Effect of food processing on vitamin D is reviewed
- Principal encapsulation techniques adopted for vitamin D encapsulation are reviewed.
- Vitamin D enriched nanomaterials for food fortification is discussed.

Abstract:

Today, as per the latest medical reports available, majority of the population throughout globe is facing vitamin D (Vit D) deficiency. Even in sub-tropical countries like India and many others Vit D deficiency is highly prevalent despite the exuberant available sunshine (a major source of Vit D) throughtout the year. The reason could be attributed to an array of factors including socioeconomic, cultural and religious Further, other than the sunlight, there are very limited sources of Vit D to fulfil the recommended dietary allowance of Vit D (RDA: 400-800 IU per

day). A large proportion of Vit D is lost during food processing and storage due to environmental stress conditions such as temperature, pH, salt, oxygen and light. Vita D, an important micronutrient, is essentially required for the prevention of disorders such as neurodegenerative diseases, cardiovascular diseases, cancer etc. in addition to its traditional role in bone metabolism. Therefore, in order to meet the daily requirements of Vit D for human body, WHO has recognized fortification as the most efficient and safest method to address malnutrition. But there are innumerable chellenges involved during food fortification using Vit D as fortificants such as homogeneity into the food matrix, physico-chemical/photochemical degradation, loss during processing and storage, interactions with other components of food matrix resulting into change in taste, texture and appearance thus affecting acceptability, palatability and marketability. Fortification of Vit D into food products especially the ones which have an aqueous portion, is not simple for food technologist. Recent advances in nanotechnology offer various microencapsulation techniques such as liposome, solid-lipid particles, nanostructured lipid carriers, emulsion, spray drying etc. which have been used to design efficient nanomaterials with desired functionality and have great potential for fortification of fortificants like Vit D. The present review is an undate on Vit D, in light of its fortification level, RDA, factors affecting its bioavailability and various microencapsulation techniques adopted to develop Vit D-nanomaterials and their fate in food fortification.

Abbreviations

Abbreviation	**Full form**
WHO	World Health Organization
FAO	Food and Agriculture Organization
IOM	Institute of Medicine
EC	European commission

UK	United Kingdom
NNR	Nordic Nutrition Recommendations
CMCS	Carboxymethyl chitosan
SPI	Soy protein isolate
WPI	Whey protein isolate
WPC	Whey protein concentrate
HACS	High amylose corn starch
MCT	Medium chain triglycerides
DMPC	1,2-dimyristoyl-sn-glycero-3-phosphocholine
PC	phosphatidylcholine

Keywords: Vitamin D, Fortification, Encapsulation, Bioavailability, Micro-/nano-encapsulation, Functional food

1. Introduction

The role of vitamin D (Vit D) in bone health (calcium and phosphorus metabolism) is well reported in literature [2, 10, 45]. This is instantiated by the fact that between 1991 and 2019, there have been approximately 80,000 published articles, listed in PubMed, which contain the term “Vit D” in their title and there has been continuous scientific activity to overcome the elusiveness of Vit D. Accruing evidences clearly show the role of Vit D in different physiological functions of the human body apart from bone health and calcium-phosphorus metabolism [45]. Hence, its insufficient intake may result into complete or partial inhibition of

those functions which may lead to osteoporosis, rickets, calcium-phosphorus imbalance, parathyroid imbalance, diabetes etc. The recent research has further elaborated the role of Vit D in prevention of cancer, cardiovascular diseases, diabetes, cellular growth, cellular differentiation, embryonic development, fertility, immunological disorder, liver disorder, neurological, renal and respiratory disorders [1-5]. Millions of preschool-aged children are found to be Vit D deficient [10]. As per the mortality reports of WHO, Vit D deficiency is one of the major contributors to total deaths (0.8 million deaths) per annum [6-9]. In infants and young children, a concentration of 25-OH-D in serum below about 11 ng/L, 20-30ng/L, $\geq$ 30ng/L, and 300 ng/L is an indication of deficiency, insufficiency, sufficiency and toxicity of Vit D respectively [9-12]. Vit D exists majority in two forms: (i) Vit D_2 (ergocalciferol), synthesized only by plants and not by human body and (ii) Vit D_3 (cholecalciferol) synthesized by the human body, especially via skin, when it exposed to sunlight (Figure 1).

There are several factors which contribute to Vit D deficiency. These includes geographical location (altitude and latitude), angle of the sun and length of the sun exposure, pollution [13, 14] and the limitation of naturally occurring Vit D rich foods. Only a few wild varieties of mushroom, certain varieties of algae from plant kingdom and foods such as egg, Cod liver oil, salmon and other fatty fish from animal kingdom are the major sources of Vit D [15, 16]. In order to meet the RDA requirements for Vit D, several countries have now permitted fortification of food with Vit D such as milk, margarine, certain edible oils, cereals etc. In addition to this, currently certain pharmaceutical supplements are also majorly being used as source of Vit D [15]. Despite the availability of Vit D fortified food, Vit D deficiency is prevailing across the globe which could be attributed to the low bioavailability of Vit D (fortified

as well as naturally occurring foods) in the food as well as in human gastro intestinal tract (GIT) [17].

1.1. Bioavailability of Vit D

The biological accessibility or bioavailability of Vit D to human body is defined as the proportion of the ingested Vit D that eventually ends in systemic blood circulations and consequently imparts related physiological functions [18]. The mechanism of absorption of Vit D (Vit D_2 and Vit D_3) is belived to be concentration independent unsaturable passive diffusion process [17]. The total quantity of Vit D present in food system does not reflects its bioavailable amount since a significant proportion remaines bound to the food matrices [18]. Unavailability of literature on the aspects of absorption and actual bioavailability of Vit D in upper GIT in human, makes it a subject of major concern. Though an array of factors influences the bioavailability of Vit D in the food system; such as variation in the physiochemical forms of the Vit D (Vit D species and the physiological linkages), the complexity of food matrice (variety and quantity of fatty acids, dietary fibers etc., doses of Vit D, location of Vit D in animal as well as plant tissue, processing condition and size of food particles) and absence/presence of Vit D enhancer/inhibitor), interaction among fat-soluble nutrients available in food and host-associated factors (surgery, age, disease, fed condition, obesity, genetic variation etc.) have been comprehensively discussed in the literature available [18].

Based upon anti-rachitic discoveries, initially it was belived that Vit D_2 and Vit D_3 were equipotent and could be used interchangeably. Nevertheless, recent scientific evidences clearly highlight the variation between their bioefficacy which is attributed to high metabolism and clearance of Vit D_2 than that of Vit D_3 in liver and kidney respectively [19]. Further, the

processing methods and conditions have also been found to have significant influence on the availability of Vit D [21-28].

Vit D is prone to degradation when exposed to heat, light, moisture, or oxygen during processing as well as storage. Thermal processing of foods such as boiling, pressure cooking, frying, steaming, baking and sterilization can significantly affect the final level of Vit D in food [21, 22]. These factors ultimately affect the actual availability of Vit D to the human body and must be considered while addressing the bioavailability of Vit D present in any food matrix. The impact of various food processing methods on Vit D content in some food products is presented in table 1.

Several methods have been adopted to determine the bioavailability such as animal model, in vitro test and bioassays [30-34]. The conclusion of bioassay generally relies on absorption/serum 25(OH)D while balance studies calculate the difference between feed (input) and excretion (output). The measurement of solubility, dispersibility, fractional permeability across the muscous membrane of GIT and Vit D uptake in the experimental animals can also be considered while selecting the in vitro studies [34, 35]. Furthermore, in vitro method is preferred over other methods due to its cost effective and rapid as compared to other methods and offers better control of experimental variables as compared to an animal or human model. However, scientific attempts are continuously in progress to develop and refine techniques to determine dietary Vit D absorption in the body. The analytical methods such as high performance liquid chromatography and liquid chromatography mass spectroscopy have been extensively used for accurate evaluation and detection of low levels of Vit D during the bioavailability studies [36, 37]

2. Supplementation and fortification of Vit D: Which is the better option?

Vit D_2 or ergocalciferol comes from Vit supplements, fortified food and some plant foods like mushrroms. Vit D_3 or cholecalciferol is synthesized and is found in animal foods like salmon, cod liver and egg yolk. It has been found that Vit D_3 more effective as compared to Vit D_2 for raising Vit D level in blood since the binding protein has a higher affinity towards Vit D_3 [11]. Supplementation and fortification are considered as the most viable options to combat Vit D deficiency [49]. Supplementation involves the use of high dose of Vit D formulations. Generally, Vit D_3 is administered in the form of cholecalciferol, alfacalcidiol, and calcitriol as solo ingredient or in combination with calcium and other minerals or vitamins. Vit D supplements containing alfacalcidiol and calcitriol are generally available in the form of tablets and capsules while the formulations containing cholecalciferol in granules in sachets [38, 39]. Cholecalciferol is the most favored form for prophylaxis and treatment of Vit D deficient states in not only India [38] but also worldwide [39]. Currently, Vit D supplement intake is voluntary and its intake is the highest among infants, elderly adults and lowest among adolescents, children and young adults who are at high risk of its deficiency. Further, the distribution of Vit D intake among population is greatly skewed to a small number of high dose supplements which poses a high risk of excessive intake [38, 39]. The procurement and purchase of Vit D normally requires quite an expensive pre-packaging, an efficient distribution system and a high level of consumer compliance (particularly if supplements are to be consumed on a long-term basis) [40]. The shortage of supplies and poor compliance are constantly reported in usually adopted supplementation program, which result into main hurdles for success. Hence, in view of public health, food processors need to work on changing the shape of Vit D intake consumption pattern with the sustainable food based strategies; concequently filling the gap between current and recommended intakes without putting the general population at risk of habitual either excessive

or difficient intake. As on today, several innovative methods have been reported for improving Vit D level in foods by fortification and biofortification.

Biofortification relies on enhancing the levels of specific, limiting micronutrients in edible tissues of plant/animal by combining crop management, breeding, and genetic approaches [16]. Studies have shown that Vit D_2 level in fungi can be significantly enhanced by exposing them to UVB light [41, 42]. Further, the stability of Vit D in these irraditated mushroom can be further improved via cold storage [43] the dried mushrooms are able to retain much of their Vit D content even after 2-6 years of cold storage [20]. A significant increase in Vit D content in animal products (pigs, fish and hens) has also been reported [44, 47]. Vit D_3 rich meat and liver can be produced by feeding pigs with Vit D_3 rich feed [16, 44]. Likewise, Vit D content in fish can also be enhanced by feeding them Vit D_3-rich feed [45] and hens which were fed on Vit D_3 rich diet have shown to produce eggs with high content of Vit D [46, 47].

Fortification of food products has been acknowledged by the World Bank (1993) as the most cost effective way for combating the nutrient deficiency problems among the available health interventions. Fortification refers as the addition of micronutrients to target foods for the purpose of its enrichemtn with respect to a given micronutrient. This strategy has resulted in relatively rapid improvements in the micronutrient status of a population at a very reasonable cost, particularly if the existing technology and local distribution networks are exploited [48, 49]. However, unfortunately, implementation of fortification programs, especially in the developing world, has been lackadaisical [50]. For this there may be several reasons including (1) lack of knowledge relevant to micronutrient deficiency status; (2) lack of understanding of the significance of micronutrient deficiencies and its concern to the healthcare system; (3)

inadequate knowledge about food consumption patterns; and (4) the consumer acceptance, competitive and costs concern of the food industry.

2.1. Present status of Vit D fortification

Several Vit D fortification programs have been implemented across the globe. The various foods fortified with Vit D so far include mostly milk, milk products, and edible oil. The food items normally selected for fortification solely depend on the consumption pattern of foods of the country's population. Many of the foods are being fortified with Vit D in conjunction with Vit A. Various reports on successful fortification of Vit D and regulatory compliance adopted for North Americans have been published [51-53]. Presently Vit D fortification has become mandatory in milk (expect goat milk and condensed milk) and margarine in Canada where it is regulated by the Canadian Food and Drug Regulations [54-60] while in USA, Vit D fortification is voluntary in fluid milk and if fortified, needs to be displayed on the label [61, 62]. It is also evident that the majority of the milk-derived products such as butter, cream, cottage cheese, sour crease, ice cream, hard and soft cheese, and yogurt are not routinely fortified with Vit D [52, 61, 63]. In addition to these products, infant formulations are being fortified globally (40-100 IU/100g) [64]. The food products that are being fortified with different level of Vit D across the globe are listed in Table 3.

Today the fortification practices adopted by different countries in the world depend upon the country's regulation. Initially, all margarine manufactured for domestic use in the UK and Ireland was subject to mandatory fortification but now it become voluntary [91]. Similarly, other foods like dried and evaporated milk, breakfast cereals, macaroni, noodles, beverages, edible oils, and wheat flour may also be voluntarily fortified with Vit D along with other micronutrients (Table 3). However, information pertaining the continuation and compliance of these

fortification regulations is very scanty [92, 93]. The stability, dispensability, and solubility of Vit D during production and storage of foods are the key concerns for food processors.

2.2. Stability of Vit D in fortified food

In general, the success of Vit D fortification mainly depends on the stability of the fat matrix in the food as Vit D is fat soluble. Fortification of Vit D has been a challenge to the food industry due to its instability and heterogeneous distribution in food. Loss of Vit D was observed in various food systems fortified with Vit D such as milk [93], cheese [97, 100,101], yogurt [102-104], and other milk based products [105, 161, 224]. The loss is mainly due to oxidation and isomerization during processing and storage [105, 106]. Similarly, Vit D found to be susceptible to oxidation with poor retention property in extruded food products also during storage [107]. Food processing methods such as baking, cooking, frying and water boiling (fish, mushroom, and egg) cause significant degradation of Vit D [21, 22, 25, 29]. In addition to the stability, uniform distribution or the homogeneity of Vit D in the fortieidfood matrix is again one of the major concern for the food industry. The stability studies in fortified foods other than milk are very limited and reports on uniform distribution are even rarer. Thus, studies addressing stability, homogenization, and bioavailability of Vit D in the fortified foods need to be conducted to gain a better understanding in designing the fortified foods.

2.3. Methods for Vit D fortification

For sustainable fortification, various techniques have been adopted such as direct addition, emulsification, and microencapsulation. In case of Vit D, direct addition is the most widely adopted method for fortification of milk and milk products [51, 52, 54]. In general, these products are being spiked with Vit D where Vit D is dissolved in food grade organic solvent (ethanol) and butter oil, and then homogenized into the food matrix to ensure the uniform

distribution [94-96]. The deposition of Vit D inside the packaging materials especially the polypacks or tetrapacks and its degradation in aqueous food matrix leading to the Vit D instability in food matrix. In emulsification method an oil phase, having Vit D, is dispersed as fine droplets in water and these fine droplets are then mixed with target food material such as cheese, milk and bread [97-99]. Homogenization of Vit D in the food matrix and limited availability of food grade emulsifiers are major challenges while developing stable emulsion.

The major challenges being faced by food technologists during fortification of Vit D are suitability of its dispersibility, homogeneity, stability and ultimately its bioavailability to the body in required doses for combating the deficiency. All theses chalanges are the driving forces leading to the development of various innovative techniques for fortifying Vit D in different food matrixs. Recent literature suggests that nanotechnology offers great stability and ensures homogeneity by encapsulation of bioactive core ingredient into a matrix with a size lower than 1000 nm. Microencapsulation is basically insulation of bioactive core material by secondary wall materials which protect the core from its external environment [108-112]. In addition to giving protection to the bioactive compound, it also helps in controlled release of encapsulant with high physiochemical stability. Microencapsulation also promises that the nanomaterials so formed would ensure high bioavailability, water dispersibility and better homogeneity of the fortificant in the target food irrespective of complexity of food matrix [111]. The rising demand for functional foods has been the major driving force for designing and production of novel nanomaterials that are suitable for fortifying the food. Literature reports several nanomaterials, which could be efficient carrier systems for Vit D for the purpose of food fortification [113]. The fortification using nanomaterials offers various advantages over direct addition and

emulsification method such as high stability, better homogeneity and improved physiochemical and organoleptic characteristics [111].

3. Use of microencapsulation techniques

The success of microencapsulation of Vit D in pharmaceuticals encouraged its application in food with the following objectives (i) beats solubility barrier between Vit D and the food matrix (ii) shields Vit D against physiochemical stress such as moisture, oxidation, pH, temperature, mechanical etc. (iii) guarantees better bioavailability with the controlled and targeted release of encapsulated Vit D (iv) does not manipulate appearance, taste, quality of food matrix, thus sustaining customer acceptability.

3.1. Status of Vit D microencapsulation

The high dispensability of lipophilic drug in aqueous media of pharmaceutical formulation made research community to assume that solubility of these lipophilic drugs can also be improved in the food matrix by microencapsulation. This assumption was evaluated by several dedicated studies such as 100-time high solubility was achieved when tretinoin was encapsulated with β-cyclodextrin [115] while it was 10000-times for anandamide [116]. However, these cyclic molecules have the ability to host Vit D molecule, but its drug loading capacity was very poor [116]. To address this problem, nanomaterials have been introduced that can offer high drug stability and encapsulation efficiency (EE). The potential of nanomaterials to become an efficient carrier is continuously ested in pharmaceutical and the food industries. Literature reports about a range of nanomaterials such as emulsion [118, 119], liposome [100, 120-132], niosome [133-137], solid lipid nanoparticles [138] and nanostructured lipid carriers [139]. Though several excellent reviews are available focusing the wall material, microencapsulation techniques, and

nanomaterials for bioactive compounds [111, 114, 140, 141] but there is a lack of dedicated reports addressing microencapsulation techniques which are exclusively used to develop Vit D nanomaterials for food application (Table 3).

3.1.1. Vit D microencapsulation using spray drying technique

Spray drying is renowned as one of the oldest technique used for bioactive compounds encapsulation. Vit D is needed to be homogenized in a dispersion containing wall materials (polymers). Then, the homogenized dispersion needs to be fed to the spray dryer and atomized by hot air that leads to the development of nanomaterials in consequence of water evaporation. The encapsulation process is subjected to a range of factors like homogeneity of dispersion system, quantity, quality and type of emulsifier used, feed rate, viscosity of dispersion system, pressure of hot air, the flow rate of hot air and inlet and outlet temperature. In spite of better control on the shape and size of nanomaterials continuous and reproducible nature, low cost, easy scale-up, spray drying is not quite popular for bioactive compounds exclusively for heat sensitive compounds [141, 173-175]. Further, several researchers have comprehensively described the key factors need to be taken under consideration during spray drying while designing nanomaterials for food application [140, 141, 176-181]. Further, spray drying offers great flexibility for choice of wall materials, one or more than one but the use of spray drying in Vit D microencapsulation is even rarer as it mandates Vit D to be in water dispersed form. Despite several advantages, the full potential of spray drying is still fully unexplored for Vit D encapsulation which could be accredited to resultant porous nanomaterials that are prone to degradation of encapsulated Vit D hence lacking the aim of encapsulation [170-172]. Vit D was encapsulated using different combinations of maltodextrin, gum arabic, modified starch and whey protein concentrate to study the effect of temperature on the physicochemical

characteristics of spray-dried whey nanoparticles encapsulating Vit D [172]. Higher stability and greater bioavailability of Vit D_2 were achieved when it was encapsulated in casein micelles using spray drying [171]. Similarly sustained release of Vit D_2 in simulated GIT conditions was demonstrated by ethylcellulose coated spray dried nanomaterials containing chitosan [170]. The stability issue can be resolved by proper selection of wall materials and association with other microencapsulation techniques.

3.1.2. Vit D microencapsulation using emulsification technique

This system involves at least two immiscible phases (lipid and water) where one phase needs to be dispersed as small spherical droplets within another phase. On the basis of the spatial arrangement of two phases, the emulsion system is generally classified into two classes i.e. oil in water (O/W) or water in oil (W/O). Then, these two immiscible phases need to be stabilized by surfactants and emulsifiers [182]. Several complex emulsion system like oil-in-water-in-oil (O/W/O), water-in-oil-in-water (W/O/W), water-in-oil-in-oil (W/O/O) or water-in-oil-in-oil-in-water (W/O/O/W), are reported in literature [183-183]. Several researchers have explored emulsion techniques to develop Vit D-nanomaterials using food grade materials such as whey protein isolate (WPI) [108], casein [149], Medium chaing triglycerides (MCT) and Tween 20, 40, 80, 85 [152], MCT and Tween 20, 60, 80 [110], carboxymethyl chitosan and SPI [151], Zein and carboxymethyl chitosan [150], Tween 20 and casein [151], WPI, calcium caseinate and sodium caseinate [98], casein [148], HACS and α-amylase [147], Tween 20 and fish oil [146], sodium caseinate and lecithin [145], quilajapaponin [118] and oleoyl alginate ester [144] and PPI [153]. Vit D emulsion fabricated sodium caseinate, calcium caseinate, nonfat dry milk, and whey protein have found to be stable during cheddar cheese preparation [98]. The selection of emulsion method for Vit D encapsulation depends on various factors such as absence/presence of

antioxidants, quantity and type of carrier oils and surfactant. It was observed that the stability of encapsulated Vit D is highly correlated to the stability of emulsion system. Further, it is also evident that the presence of an antioxidant in the emulsion system also enhances the stability of Vit D.

3.1.3. Vit D microencapsulation using liposome

Literature reveled about various preparation methods for liposome which are comprehensively discussed by researchers in their excellent reviews [131, 136, 186-192]. In general, liposomes are referred to the spherical liquid structures in which an aqueous core bounded by a single (unilamellar liposomes) or multiple lipid bilayers (multilamellar liposomes). The ability to host both hydrophilic and hydrophobic bioactive ingredients individually or simultaneously makes liposome the most adopted encapsulation technique for Vit D. In addition to flexibility in composition and size, liposome also promises high biocompatibility with animal tissue as it mimics with the natural plasma membrane [188]. Several researchers have fabricated liposome for encapsulation of Vit D using 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) [130], methylparaben and propylparaben and the di-sodium edentate [129], L-α-phosphatidylcholine and L-α phosphatidyl-DL glycerol [120], 1-O-Octadecyl-2-O-benzyl-3-methylthio-1,2-propanediol [121], phosphatidylcholine [100], hydrogenated phosphatidylcholine [123] and soybean phosphatidylcholine [127]. Though, Vit D shows high chemical stability when it is integrated within liposome but its application in food fortification is still not fully explored. The limited use of liposome in Vit D fortification could be attributed to its dependency on soya derived lecithin which carries intense smell. This issue can be easily resolved by replacing soya derived lecithin with milk-based lecithin or hydrogenated lecithin.

3.1.4. Vit D microencapsulation using solid lipid nanoparticles

It is referred as the most suitable encapsulation technique for vitamins encapsulation as it has the hybrid structure of liposome and emulsion system hence tenders a range of advantages like high drug loading capacity, higher encapsulation efficiency, and better chemical stability against physiochemical stress. The literature describes the preparation methods for solid lipid nanoparticles (SLN) [136, 137, 193-201]. The ability of SLN to encapsulate and protect Vit D is still untapped and the only single report has been generated till date in which Vit D-SLN was prepared using molten tripalmitin [201].

3.1.5. Vit D microencapsulation using nanostructured lipid carriers (NLC)

NLC generally encompasses ~~of~~ unstructured solid lipid matrix comprised of a mixture of liquid and solid lipid blend and an aqueous phase consisting of a surfactant or a mixture of surfactants. Typically, liquid and solid lipids are blended in a ratio that could vary from 70:30 to 99.90:0.10 while the surfactant content is kept between 1.5-5% (W/V) [202]. The unstructured/partially solid matrix creates interesting nanostructures, which enhance the stability of the entrapped bioactive compound, facilitate high loading capacity and offers controlled/target release. Literature dictates various methods for NLC preparations [202-205]. Despite being the most promising technique for drug delivery, NLC is among the least explored method for Vit D encapsulation. Till date, only three dedicated studies were reported addressing Vit D encapsulation in NLC [139, 143, 224]. In the first report, Vit D loaded NLC was formulated by phase-inversion temperature method displayed high physical and chemical stability for NLC as well as Vit D and was found to be a suitable vehicle for milk fortification [139]. While the second report was conducted to evaluate the drug release kinetic of Vit D loaded NLC and were fabricated with oleic acid, glycerol monosterate and Tween 80 using hot high-pressure

homogenization [143]. NLC particles displayed biphasic kinetic release (burst effect) resulting in almost 50% of the Vit D released during the first 2 h and 80% released after 4 h of digestion, followed by a sustained release until 90.9% of the Vit D during 8 h [143].

3.1.6. Vit D microencapsulation using molecular complex

In general, the molecular complex is formed with the use of cyclodextrin which can host bioactive agents within its void. Cyclodextrin is usually applied for encapsulation of Vit D in pharmaceutical formulations to assess its chemical stability against various physiochemical stresses [117, 119, 144, 153, 167].

3.1.7. Vit D microencapsulation using electrospinning

It is a fiber producing technique which exertes electric force to draw charged fiber of polymer solutions or polymer melts up to diameters of nanoscale. This continuous process is performed by extruding dispersion of polymer through the needle on rotating drums to impact charge on fibers. The literature describes electrospinning as the most suitable techniques for thermo-sensitive bioactive agents, but its use for Vit D encapsulation is very scant. Till date single report is documented in which Vit D-nanofiber fabricated using poly (vinyl pyrrolidone) [169].

3.2. The fate of Vit D-nanoscale materials in GIT

The small intestine is recognized as the site of absorption of Vit D after its oral ingestion [206, 207]. Figure 2 illustrates the main routes of Vit D absorption in small intestine. Nanomaterials encapsulating Vit D have demonstrated its improved absorption [114, 122, 139, 161] and the mechanism how nanomaterials improve its oral bioavailability has already been reviewed in the previous article [114]. Generally, mixed micelles are generated as a result of digestion of lipid as well as nanomaterials and facilitate Vit D passage passing through the aqueous mucous layer to make it bioavailable to brush bordered enterocytes. The absorbed Vit D is then encased into

chylomicrons within the enterocytes depending on their hydrophobicity [208, 209]. The chylomicrons and lipid particles are endogenously produced within the enterocytes using lipid components (monoacyglycerols, free fatty acids, and sterol) of mixed micelles [210]. Then the chylomicrons incorporating Vit D are transported to the lymphatic circulation system via chylomicron-mediated pathway.

In parallel, it is also assumed that a fraction of Vit D still retained within nanomaterials rather being released during digestion [211, 212]. Vit D-nanomaterials are speculated to pass paracellularly to the portal blood via tight junctions or taken up by M cells via Peyer's patches followed by excretion into the lymph. In addition, it is also supposed that the structure and integrity of intestinal border can be modulated with nanomaterials containing specific compounds hence changing Vit D absorption efficiency. The literature reports about these compounds which can modulate the intestinal epithelial integrity such as surfactants (modulate the integrity of the plasma membrane), EDTA (widens intracellular tight junction seals), chitosan (separate the tight junction components) and free fatty acids (increases plasma membrane permeability) [114]. The use of these materials during nanomaterials preparation may help in achieving the desired functionality.

3.3. Vit D fortification with nanomaterials

To our knowledge, a significant numbers of food products are fortified with Vit D either mandatorily or voluntarily [222]. The current fortification method uses direct addition/mixing of Vit D in food matrices which may carry various limitations like loss of activity, degradation, irregular distribution, inevitable undesirable interaction, change in appearance and taste, hence affecting the customer acceptability. Microencapsulation is a tested technique to address these

issues, but it remained untapped for Vit D encapsulation for fortification purpose. The first use of microencapsulation technique in the food was initiated with Indyk's study where high stability of Vit D was achieved by encapsulating Vit D in milk powder using spray drying [106]. Further, liposome incorporated with Vit D was applied for fortification for cheddar cheese [97, 100]. Conversely, the high stability of Vit D was reported in soybean phosphatidylcholine based liposome which was found to suitable nanomaterial for food fortification [127]. Likewise, Tippetts' team has developed Vit D premix and applied it for the production of Vit D enriched artificial rice [98]. Further, the re-assembled casein based micelles encapsulating Vit A and D displayed great stability during the storage period and were compatible with milk fortification [203]. In addition, Kiani's team fortified milk with NLC that didn't change the color and texture of milk [139]. Moreover, Vit D rich nanoemulsion was developed using phase inversion based method to evaluate its feasibility in buttermilk fortification [161].

Above observations clearly indicates that desired stability, bioavailability and dispersibility can be achieved by encapsulating Vit D by one or more than one encapsulation techniques mentioned above. Further, high bioavailability of Vit D is reported when Vit D is administered through mushroom [214, 215]. Hence, it will be rationale for further research to exploiting these observations to design Vit D rich food with desired functionalities. Figure 3 describes the systematic approach for the development of Vit D rich functional foods with its improved bioavailability.

3.4. Safety concerns and risks of Vit D nanoparticles

In general, the nanomaterials are adopted to improve the oral bioavailability of poorly soluble drugs. The available reports clearly indicate that the uptake of nanomaterials from the GIT tract is subjected to its particle size [216] and surface properties [217]. Similarly modified

characteristics of nanomaterials such as particles size and penetration ability to cross the physical barrier and ability to modulate cell integrity may transmit undetected risk to the biological system. Utilization of biodegradable or natural materials may limit health hazards which could generally posed by synthetic polymeric nanomaterials. Due to uncertainty in the long or short term and the direct or indirect effect of nanomaterials based foods, it is significant to assess the effect of nanomaterials on human health [218]. In view of food safety, Food and Drug Administration (FDA) has planned special strategies for mass production of food and food components incorporated with nanomaterials [219, 220]. Anyway, there are no definite legislative guidelines framed addressing the use of nanomaterials in food supply, however, several agencies and government bodies claim to follow the safety concerns of nanomaterials based food products [221]. The tentative guidelines can be drafted with list of suggestions (i) the physiochemical characterization nanomaterials applied in the food (ii) characterization process to assess their hazards characteristic embraced by nanomaterials such long and short term toxicity assay (iii) submission of a toxicity assessment report to legislative bodies such as FDA, Food Safety and Standard Authority of India (FSSAI), European Union (EU) etc. (iv) recognize and state a regulatory compliance for the consumption of the nanomaterials derived foods. However, lack of precise guidelines regarding the use of nanomaterials in food, demands various legislative bodies to come up together to frame universal guidelines which could be applicable across the globe.

4. Conclusion

Despite the fact that the endogenous synthesis of Vit D can able suffice its daily requirement, its deficiency is prevailing across the globe which could be attributed to various factors such awareness, socioeconomic, cultural and religious constraints and lack of diversity in Vit D rich

foods. These factors equally contribute to the determination of its RDA and fortification level, which are subject to the country's regulations. Fortification is considered as the most effective among the available health interventions, but it brings inevitable interactions with food components resulting in the loss during food processing and storage. Vit D bioavailability in food can be improved either through its direct fortification or by the use of Vit D-nanomaterials in processed foods. Microencapsulation seems to be an indispensable tool to design Vit D-nanomaterials with desired functionality such as high stability against photochemical and mechanical stress, better homogeneity with the food system, improved oral bioavailability, avoidance the overdosing and improved organoleptic properties. Rationale knowledge about Vit D in the view of its chemistry, source, factors influencing its deficiency as well as bioavailability, RDA and fortification level, and microencapsulation techniques may aid better understanding in the designing of novel nanomaterialswith desiredproperties for food fortification.

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Legends:

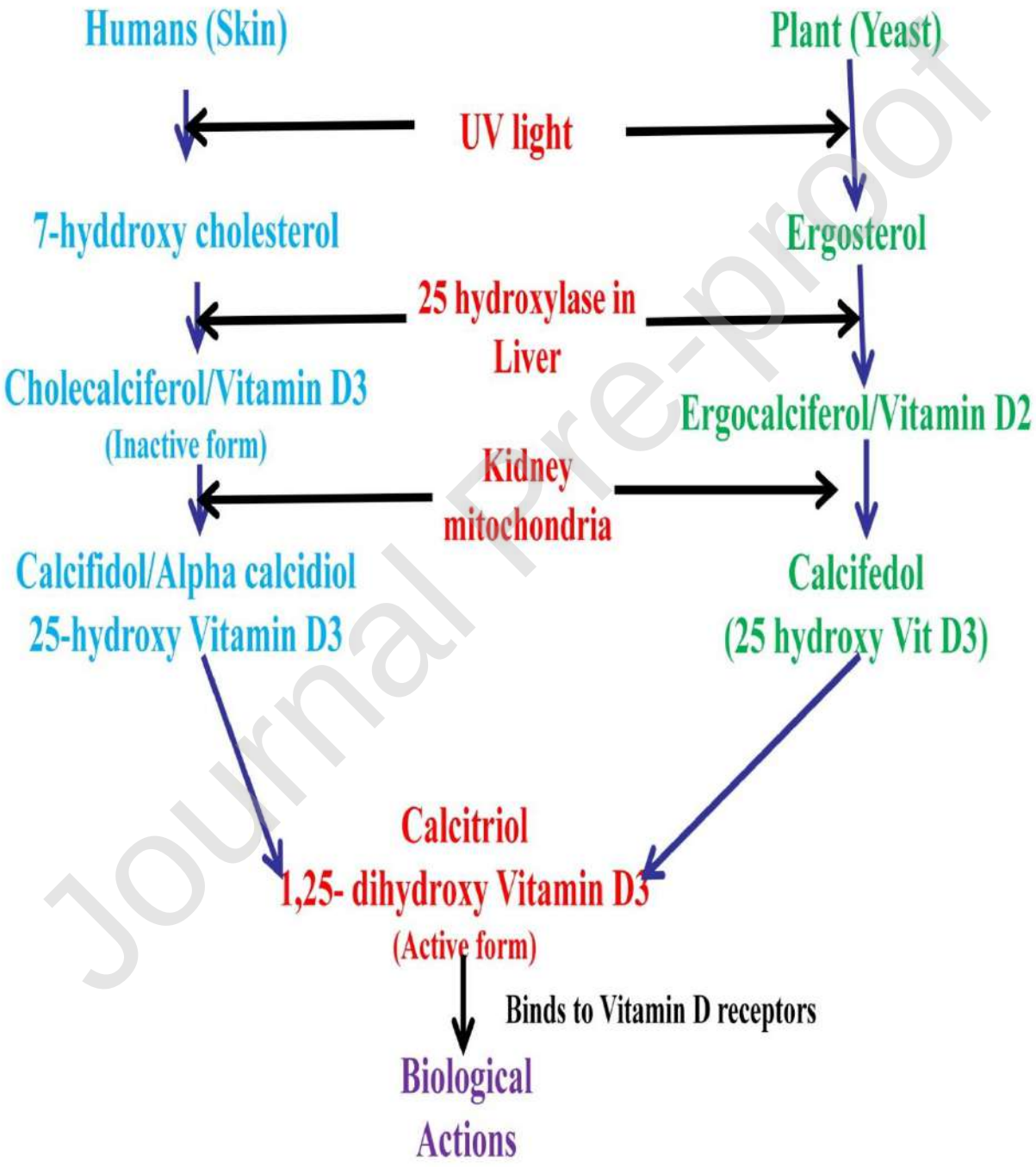

Figure 1. Vitamin D synthesis pathway

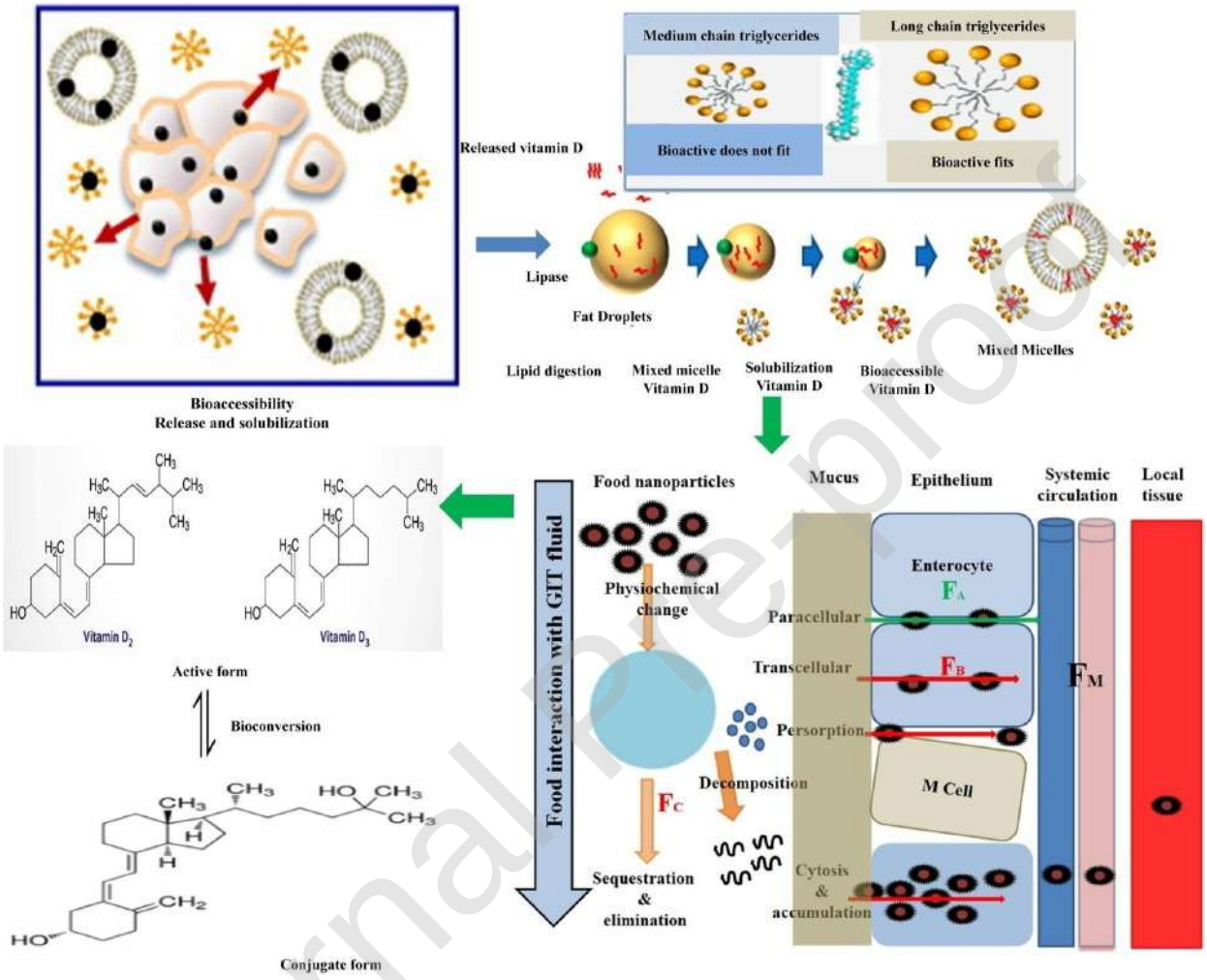

Figure 2: Physiochemical and physiological processes involved in digestion and absorption of vitamin D in GIT. The fate of vitamin D based nanoscle materials in intestinal lumen. Where **F_B:** fraction of the encapsulated vitamin D which released from food matrix into the gastric juice in GIT, **F_A:** fraction of the vitamin D which is transported through the intestinal epithelium and then transported to the portal or lymph, **F_M:** The fraction absorbed vitamin D which is an active form after bypass the chemical modification by organs such as liver and kidney

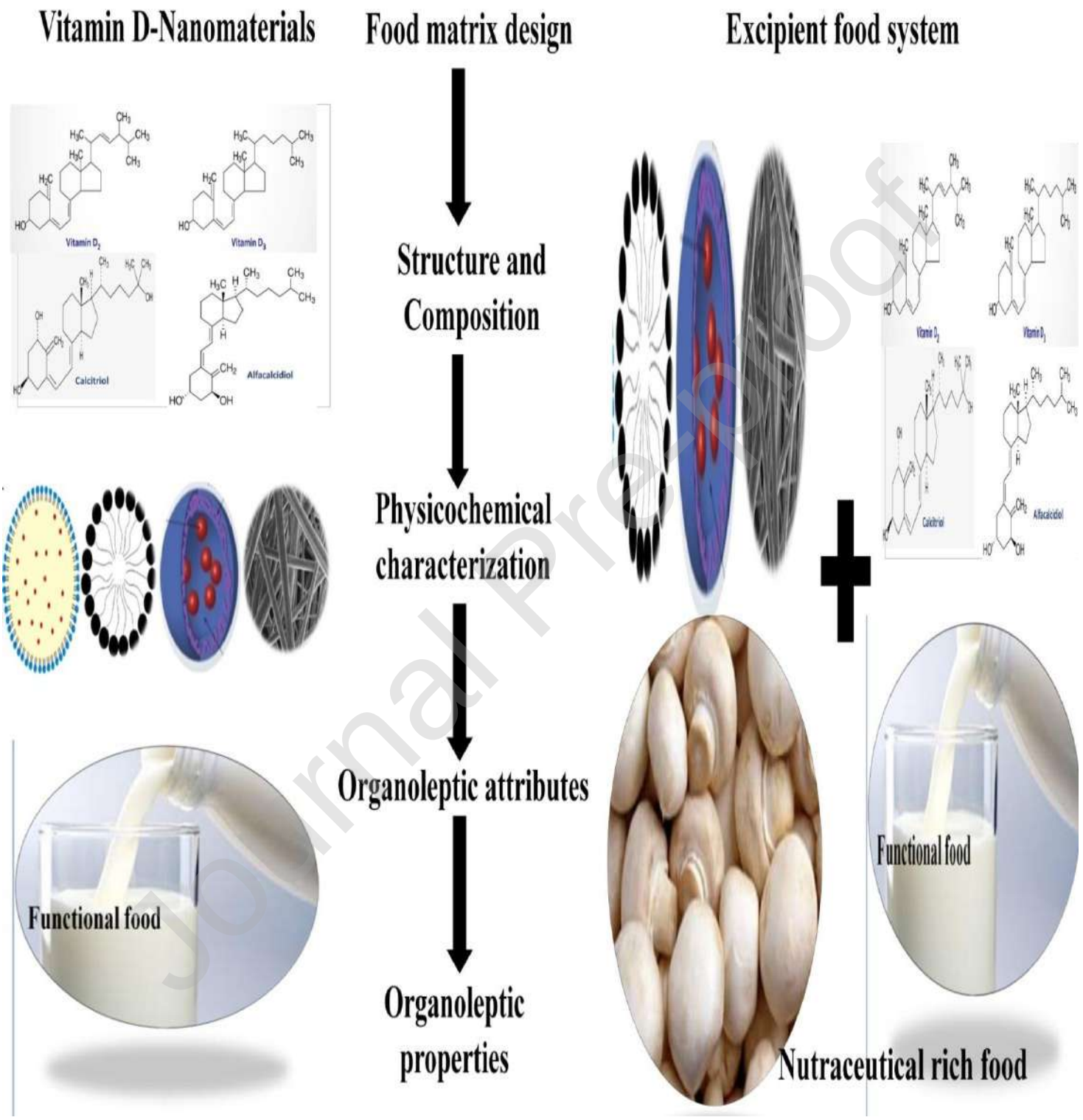

Figure 3. Fortification strategy for development of vitamin D enriched food system

Table 1: Effect of processing practices on vitamin D

Food processing	**Food**	**Impact on vitamin D**	**Reference**
Baking	Fish, meat	Significant reduction in cholecalciferol	[23, 24]
	Bread	24-31% loss in ergocalciferol	[22]
Boiling	Egg	Significant loss in25-hydroxycholecalciferol	[23]
		22-24% loss in vitamin D	[22]
Frying	Mushroom	Significant loss in ergocalciferol	[23]
	Egg and Margarine	22-24% loss in vitamin D	[22]
Cooking	Beef	35–42% of the original vitamin D	[21]
Pasteurization	Milk	No significant loss	[25]
Sterilization	Milk	No significant loss	[25]
Solar Drying	Fish meat	Significant loss	[26]
Steaming	Fish oil	Significant loss	[27]
Oven Drying	fish meal	Significant loss	[28]
Smoking	Fish	Significant loss	[29]
Roasting	Beef	Significant loss	[21]

Table 2: Vitamin D fortified foods and fortification level across the globe, where * is signifies to mandatory fortification

Country	Category	Food name	Fortification level	Reference
			For adults	
USA	Dairy	Fluid milk	400 IU/ 946 mL	[52, 61, 65, 222]
		Acidified milk	400 IU/ 946 mL	
		Cultured milk	400 IU/ 946 mL	
		Concentrated milk	400 IU/ 946 mL	
		Evaporated milk, fortified	89 IU/100 g	
		Evaporated milk	89 IU/100 g	
		Dry whole milk	89 IU/100 g	
		Yogurt	89 IU/100 g	
		Low fat yogurt	89 IU/100 g	
		Nonfat yogurt	89 IU/100 g	
		Margarine	89 IU/100 g	
		Cheese and cheese products (excluding cottage cheese, ricotta cheese, and hard grating cheeses)	81 IU/30g	
		Calcium-fortified fruit juices and drinks	100 IU/RACC	
	Cereals	Enriched Farina	>350 IU/100 g	
		Enriched rice	550–2200 IU/kg	
		Ready-to-eat breakfast cereals	350 IU/100 g	
		Enriched macaroni products	89 IU/100g	
		Enriched farina	≥550 IU/kg	
		Enriched noodle	90 IU/100g	

		products		
		Enriched vegetable macaroni products	550–2200 IU/kg	
		Enriched vegetable noodle products	550–2200 IU/kg	
	Other foods	Special dietary meal replacement bars or other type bars	100 IU/ 40g	
	Beverages	Orange juice	100 IU/240 ml	
		Malted drink mix and powder	123 IU/g	
		Special dietary soy-protein based meal replacement beverages	140 IU /240ml	
Canada	Dairy	Milk, milk powder, sterilized milk, (naming the flavour) milk*	300-400 IU/100g	[52, 66-69, 222]
		Condensed milk	Optional	
		*Skim milk with added milk solids, partly skimmed milk with added milk solids, (naming the flavour) skim milk, (naming the flavour) partly skimmed milk, (naming the flavour) skim milk with added milk solids, (naming the flavour) partly skimmed milk with added milk solids, skim milk, partly skimmed milk, skim milk powder	300-400 IU/100g	

		*Evaporated skim milk, concentrated skim milk, evaporated partly skim milk, concentrated partly skimmed milk	300-400 IU/100g	
		Food represented for use in a very low-energy diet*	300-400 IU/100g	
		Meal replacements and nutritional supplements	300-400 IU/100g	
		Goat's milk, goat's milk powder	Optional	
		Partly skimmed goat's milk, skimmed goat's milk, partly skimmed goat's milk powder, skimmed goat's milk powder	300-400 IU/100g	
		Evaporated goat's milk	Optional	
		Evaporated partly skimmed goat's milk, evaporated skimmed goat's milk	Optional	
		Margarine*	530 IU/100 g	
	Other foods	ǂLiquid whole egg, dried whole egg, frozen whole egg, liquid yolk, dried yolk, frozen yolk, liquid egg white (liquid albumen), dried egg white (dried albumen), liquid whole egg mix, dried whole egg mix, frozen whole egg mix,	Optional	

		liquid yolk mix, dried yolk mix, frozen yolk mix		
		Infant formulas and formulated liquid diets	530 IU/100 g	
Latin America				
Brazil	Dairy	Dried skimmed milk	2000–2400 IU/kg	[52, 66-69]
Guatemala	Dairy	Skim milk	400–600 IU/L	
		Whole milk	400–600 IU/L	
Honduras	Dairy	Milk	400 IU/L	
		Margarine	1500 IU/kg	
Mexico	Dairy	Sterilized low-fat milk	400 IU/L	[52, 66-69]
		Pasteurized low-fat	400 IU/L	
		Milk	NA	
		Evaporated whole	400 IU/L	
		Margarine/Spreads	2000 IU/kg	
Argentina	Dairy	Fluid and dried	400 IU/L	[65]

Panama	Dairy	Margarine	1500 IU/kg	[70]
Ecuador	Dairy	Margarine	2000-4000 IU/kg	[52, 66-69]
Peru	Dairy	Margarine	3000 IU/kg	[70]
Venezuela	Dairy	Dried milk powder	400 IU/L	[70]
Chile	Dairy	Margarine	3000 IU/kg	[70]
Colombia	Dairy	Margarine*	200-400 IU/100g	[69. 70]
Uruguay	Cereals	Rice	NA	[69]
Ecuador	Dairy	Margarine*	200-400 IU/100g	[69]
Australia and New Zealand				
New Zealand	Dairy	Edible oils and spreads Edible oil spreads and margarine:	40-164 IU/10g	[71]
	Beverages	Formulated Beverages	100 IU/10g	
		Beverages containing no less than 3% m/m protein derived from legumes	40-164 IU/200ml	
		Analogues of yoghurt and dairy desserts containing no less than 3.1% m/m protein derived from legumes		
		Analogues of cheese containing no less than 15% m/m protein derived from legumes	40-164 IU /150g	
	Analogue Beverages	Orange juice	44-123 IU/g	

	Analogues derived from cereals	Beverages	40-164 IU/25g	
Australia	Dairy	Edible oil spreads	220-640 IU/100g	
	Cereals	Breakfast cereals	100 IU/serving	
Europe				
UK	Beverage	Orange beverage	1000 IU/240ml	[69, 72-75, 222]
	Dairy	Margarine	282–352.8 IU/100 g	
	Cereals	Bread	200 IU/100g	
		Infant formula	NA	
Austria	Dairy	Milk	NA	
Bulgaria	Dairy	Milk	NA	
Estonia	Dairy	Milk	NA	
France	Dairy	Milk	NA	
Germany	Oil	D-fluorette in first few months of life	NA	
Iceland	Dairy (Voluantary)	1.5% fat milk	20 IU/100g	
		0.3% fat milk	15.2 IU/100g	
Sweden	Dairy	*Milk with ,3% fat	38-44 IU/100g	
		*Lactose free/vegetable based milk alternative	38-44 IU/100g	
		*Sour milk products with <3% fat	11-44 IU/100g	
		*Lactose free/vegetable based sour milk alternative	11-44 IU/100g	
		*Margarine, fat spread and fluid margarines	780-840 IU/100g	

Norway	Diary	Extra low fat milk	16 IU/100g	
		Lactose free milk	16 IU/100g	
		Margarine	32 IU/100g	
		Butter	32 IU/100g	
The Netherlands	Cereals	Porridge cereals	200 IU–649 IU/100g	
		Breakfast cereals	68 IU–400 IU/100g	
	Cookies	Infant cookies	120 IU–400 IU/100g	
	Dairy	(Fruit) fromagefrais	38 IU–50 IU/100g	
		Ready-to-drink milk porridge	40 IU-80 IU/100g	
		Yoghurt drink	30 IU/g	
		Toddler milk	38–38 IU/g	
	Drinks	Instant cacao powder	320 IU/100g	
		Soja drink junior	29.6 IU/100g	
Finland	Dairy	Milk (except organic milk)*	40 IU/100g	
		Sour milk*	40 IU/100g	
		Yoghurt*	40 IU/100g	
		Vegetable based milk alternative	40 IU/100g	
		Margarine	800 IU/100g	
		Fat spreads	800 IU/100g	
Turkey		Rice	NA	[69]
Asia				
Philippines	Dairy	Filled milk, sweetened	≥973IU/L	[76-79]
		Margarine	3300 IU/kg	
Saudi Arabia	Cereals	Enriched wheat and	≥551.15 IU/kg	[80]
Bahrain	Cereals	Enriched and enriched	≥551.15 IU/kg	
Morocco		Margarine	250-300 IU/100g	[79]
		Rice	NA	[69]
Sri Lanka		Margarine	300 IU/100g	[69]
India	Oil	Vanaspati	44 IU– 64 IU/100g	[48]

		Edible oil	44 IU– 64 IU/100g	
	Dairy	Milk	200 -300 IU/L	
Indonesia		Margarine*	2500-3500 IU/kg	
Thialand		Sweetened condensed milk*		[70, 77-79, 81-89]
Malaysia	Dairy	Condensed milk	111 IU/100 g	
		Malted milk Powder	667 IU/100g	
		Liquid foods	100 IU/100g	
		Dried milk	333 IU/100g	
	Cereals	Bread	83 IU/100g	
		Breakfast cereals	333 IU/100g	
		Wheat Flour	167 IU/100g	
		Extract of meat	2000 IU/100g	
		Other solid food	167 IU/100g	
Singapore		Food not specified	400 IU/serving	
Brunei Darussalam		Food not specified	50 IU/ serving	
Africa				
Zimbabwe		Cooking oil	NA	[70, 90]
Nigeria		Margarine	NA	[69]

Table 3: Microencapsulation techniques widely adopted for development of vitamin D-nanomaterials

Microencapsulation techniques	**Preparation method**	**Matrix composition**	**References**
Liposome	Homogenization	Phosphatidylcholine	[97]
	Thin film hydration method	L-α-Phosphatidylcholine, L-αphosphatidyl - DL glycerol sodium salt	[120]
	Thin film hydration method	1-O-Octadecyl-2-O-benzyl-3-methylthio-1,2-propanediol	[121]
	Supercritical antisolvent-based Technology	Hydrogenated phosphatidylcholine	[123]
	Film hydration-sonication technique	Soybean phosphatidylcholine	[127]
	Homogenization	Methylparaben and propylparaben and disodium edetate	[129]
	Film hydration-sonication technique	1,2-dimyristoyl-sn-glycero-3-phosphocholine	[130]
	Hydration	Xanthan and guar gums	[142]
Solid lipid nanoparticles	Hot homogenization technique	Glyceryl tri palmitate, Polyoxyethylene and Sorbitanmonolaurate	[138]
Nanostructured lipid carriers	Phase-inversion temperature	Capric and caprylic acid triglyceride, Polyethylene glycol hydroxyl stearate and Soybean lecithin	[139]
	Phase-inversion temperature	Oleic acid, Glycerol monostearate and Tween 80	[143]
Emulsion system	Microchannel emulsification	Tween 20 and decaglycerolmonolaurate (Sunsoft A-12) or β-lactoglobulin.	[119]
	Homogenizing	Oleoyl alginate ester	[144]
	Homogenizing	Quillajasaponin, Triglycerides in MCT	[118]

	Homogenization method	Sodium caseinate, Lecithin, Decaglycerolmonooleate	[145]
	Wash out Method followed by ultrasonication	Tween 20, Fish oil	[146]
	Solvent evaporation assisted lyophilization	*N*,*N*-dimethylhexadecylcarboxymethyl chitosan.	[223]
	Sonication	High amylose corn starch and Alpha-amylase	[147]
	Acidification assisted with ultrasonication	Whey protein isolate	[108]
	High pressure treatment	Casein	[148]
	Microfluidization	Whey protein concentrate, Calcium caseinate and Sodium caseinate	[98]
	Acidification	B-casein	[149]
	Ultra-high-pressure homogenization	Tween-80 and Casein	[112]
	Phase Separation method assisted lyophilization	Zein and Carboxymethyl chitosan	[150]
	Isoelectric precipitation	Carboxymethyl chitosan and Soy protein isolate	[151]
	Micro fluidization	Tween 20, 60 or 80 and Medium chain triglycerides	[110]
	Spontaneous emulsification	MCT oil, Tween- 20, 40, 60, 80 and 85	[152]
	Sonication	Pea protein isolate	[153]
	High pressure homogenization	Orange oil, starch and miglyol 812	[154]
	High pressure homogenization	Soybean oil/ olive oil/or medium chain triglyceride and Tween 20	[155]
	High-pressure homogenization	Cellulose	[156]
	Ultra-high-pressure homogenization	Casein	[157]
	Microfluidization	Corn oil and tween 80	[158]
	High pressure homogenization	Polysorbate 20, tween 20 and soybean lecithin	[159]

	High-pressure homogenization	Corn/fish/ flaxseed oil and pea protein	[160]
	Phase inversion	Caprylic-/capric triglyceride, Leciva S70, Kolliphor® HS 15	[161]
	pH-shifting and sonication combined treatment	Pea protein isolate	[162]
	Sonication and ph-shifting	Pea protein isolate	[153]
	Homogenization	Corn oil and whey protein isolate	[163]
Molecular complexes	Chemical modification	Cyclodextrin, Strontium salt	[164]
	Solvent evaporation method	*β*-cyclodextrin	[165]
	Solvent evaporation method	*β*-cyclodextrin	[117]
	Solvent evaporation method	*β*-cyclodextrin	[166]
	Chemical modification	Bisphosphonate, cyclodextrin	[167]
	Sonication	Amylose and amylopectin	[168]
	Complex coacervation	Carbohydrate (cress seed mucilage, CSM) and a protein (gelatin)	[162]
Electrospinning	-	Polyvinylpyrrolidone	[169]
Spray drying	-	Chitosan	[170]
	-	Casein	[171]
	-	Whey protein	[172]